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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,432	01/05/2001	William A. Bachovchin	TUU-P02-006	3173

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,432	BACHOVCHIN ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 15, 2003 has been entered.

2. Claims 2, 11, and 26 are objected to because of the following informalities: At claim 2, page 7, line 1, "or" should be deleted. At claim 11, line 1, the comma after "4" should be deleted. At claim 26, page 16, line 6, a comma should be inserted after the last chemical structure in the line. Appropriate correction is required.

3. Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The definition of R_{11} and R_{12} in claim 24 indicating that the substituent can be hydrogen is not embraced by the definition of Y_1 and Y_2 in claim 16, which does not permit boron to be substituted with hydroxyl groups.

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Formula (II) as recited in amended claim 28 is not recited in the specification.

5. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v.*

Eagle Mfg. Co., 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 30 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of (re-numbered) claim 67 of copending Application No. 10/190,267. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-14 and 16-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-42 and 46-68 of copending Application No. 09/628,225. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '225 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-14 and 16-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-132 of copending Application No. 10/190,267. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '267 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. The effective filing date of instant claims 1-14 and 16-40 is deemed to be February 2, 1998, the filing date of provisional application 60/073,409. Instant claims 1-14 and 16-40 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the parent provisional application because the parent provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention. Accordingly, the Deacon et al article (Diabetes, Vol. 47, pages 764-769) and the WO Patent Application 98/25644 are not available as prior art against these claims. (Drucker, U.S. Patent No. 5,952,301, in the same patent family as the WO Patent Application '644, is not applied against the instant claims because Drucker does not contain any disclosure concerning the use of dipeptidylpeptidase inhibitors.)

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 1-3, 5-13, 16, 20, 21, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 95/15309. The WO Patent Application '309 teaches administering DPIV inhibitors to treat human disease. The inhibitors are highly potent, with Ki values ranging into the nanomolar range or less, and are chemically stable. The DPIV inhibitors

with the smallest Ki have the same structure as is set forth in Applicants' claims 15, 16, 20, 21, and 25. See, e.g., page 3, lines 10-21; page 4, lines 1-3; compounds 38-40; and Table 9. Because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1, glucose metabolism, insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia, and peptide hormone metabolism will be modified to the same extent in the method of the WO Patent Application '309 as is claimed by Applicants. With respect to instant claims 8-10, in view of the similarity in structure and function between the DPIV inhibitor of the WO Patent Application '309 and Applicants' claimed DPIV inhibitor, the EC50's and Ki for the DPIV inhibitor of the WO Patent Application '309 will inherently be the same as is recited in instant claims 8-10. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitor of the WO Patent Application '309 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of the WO Patent Application '309.

12. Claims 1-3, 5-13, 16, 20, 21, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 95/15309 as applied against claims 1-3, 5-13, 16, 20, 21 and 25 above, and further in view of the Kieffer et al article (Endocrinology, Vol. 136, pages 3585-3596) or the Mentlein et al article (Eur. J. Biochem., Vol. 214, pages 829-835). The WO Patent Application '309 does not explicitly state that its process results in reducing the rate of metabolism of GLP-1. The Kieffer et al article and the Mentlein et al article disclose that GLP-1(7-36)NH_2, the active form of GLP-1, is degraded in vivo by DPIV. Therefore, it would have been expected that administering a DPIV inhibitor in vivo, as is taught by the WO Patent

Application '309, would result in inhibition of the actions of DPIV in vivo, including degradation of GLP-1(7-36)NH_2. The Kieffer et al article and the Mentlein et al article are further evidence that the method taught by the WO Patent Application '309 inherently results in reducing the rate of metabolism of GLP-1 in vivo and therefore anticipates Applicants' claims.

13. Claims 1-3, 5-14, 16-24, 26, 27, 29-37, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 93/08259. The WO Patent Application '259 teaches inhibiting the enzymatic activity of DPIV in a mammal by administering a peptide compound. The peptides compounds are proteolyzed by DPIV in vivo until a C-terminal dipeptide portion remains, which acts as an inhibitor of DPIV. The peptide compound is more stable in vivo than the C-terminal dipeptide portion. If the C-terminal dipeptide portion is chosen to be a dipeptide prolyl-boronic acid, then a potent and highly specific inhibitor having a Ki in the nanomolar range is ultimately released in vivo. Tetrapeptides comprising Ala-boroPro and Pro-boroPro as the C-terminal dipeptide portions are taught, as are boroPro analogues comprising groups capable of being hydrolyzed to form hydroxyl groups. As an alternative to the boroPro group, trifluoroalkyl ketone groups are taught. The compounds can be administered orally, in amounts up to 1-500 mg/kg/day. See, e.g., page 2, lines 15-32; page 3, line 1 - page 7, line 16; page 14, lines 10-12; page 14, line 34 - page 15, line 16; and page 21, lines 14-15 and 29-30. Because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1, glucose metabolism, insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia, and peptide hormone metabolism will be modified to the same extent in the method of the WO Patent Application '259 as is claimed by Applicants. With respect to

instant claims 8-11 and 33-35, in view of the similarity in structure and function between the DPIV inhibitors of the WO Patent Application '259 and Applicants' claimed DPIV inhibitors, the EC50's and Ki's for the DPIV inhibitors of the WO Patent Application '259 will inherently be the same as is recited in instant claims 8-11 and 33-35. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitors of the WO Patent Application '259 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of the WO Patent Application '259.

14. Claims 1-3, 5-14, 16-24, 26, 27, 29-37, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 93/08259 as applied against claims 1-3, 5-14, 16-24, 26, 27, 29-37, 39, and 40 above, and further in view of the Kieffer et al article (Endocrinology, Vol. 136, pages 3585-3596), the Mentlein et al article (Eur. J. Biochem., Vol. 214, pages 829-835), or Drucker et al (U.S. Patent No. 6,184,201). The WO Patent Application '259 does not explicitly state that its process results in reducing the rate of metabolism of GLP-1. The Kieffer et al article and the Mentlein et al article disclose that GLP-1(7-36)NH_2, the active form of GLP-1, is degraded in vivo by DPIV. Drucker et al disclose that GLP-2 is degraded in vivo by DPIV (see, e.g., column 6, lines 32-33). Therefore, it would have been expected that administering a DPIV inhibitor in vivo, as is taught by the WO Patent Application '259, would result in inhibition of the actions of DPIV in vivo, including degradation of GLP-1(7-36)NH_2 and of GLP-2. The Kieffer et al article, the Mentlein et al article, and Drucker et al are further evidence that the method taught by the WO Patent Application '259 inherently results in

reducing the rate of metabolism of GLP-1 and GLP-2 in vivo and therefore anticipates Applicants' claims.

15. Claims 1-13, 16, 20, 21, 25, and 38 are rejected under 35 U.S.C. 103(a) as being obvious over the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) in view of the WO Patent Application 95/15309 and further in view of Efendic et al (U.S. Patent No. 5,631,224). The Balkan et al abstract teaches improving the glucose tolerance of insulin resistant, glucose intolerant, obese Zucker rats by administering the DPP-IV inhibitor SDZ 272-070 (i.e. valine pyrrolidide). The inhibitor prevents inactivation of endogenous GLP-1. The Balkan et al abstract does not disclose the use of DPIV inhibitors having a Ki and an EC_{50} as recited in claims 8-11 or having the structure recited in instant claims 1, 2, 4, 16, 20, 21, and 25. The WO Patent Application '309 teaches administering DPIV inhibitors to treat human disease. The inhibitors are highly potent, with Ki values ranging into the nanomolar range or less, and are chemically stable. The DPIV inhibitors with the smallest Ki have the same structure as is set forth in Applicants' claims 1, 2, 4, 16, 20, 21, and 25. See, e.g., page 3, lines 10-21; page 4, lines 1-3; compounds 38-40; and Table 9. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the DPIV inhibitors of the WO Patent Application '309 in the method of the Balkan et al abstract because the DPIV inhibitors of the WO Patent Application '309 have the advantage of having a low Ki and of having chemical stability, which would permit the use of smaller dosages of the active agent, because the DPIV inhibitors of the WO Patent Application '309 are described as being generally useful as inhibitors of DPIV-mediated processes (see, e.g., the Abstract), and because the method of the Balkan et al abstract operates via a DPIV-mediated process. It would have been obvious to one

of ordinary skill in the art at the time Applicants' invention was made to choose DPIV inhibitors from the WO Patent Application '309 for use in the methods of the Balkan et al abstract so as to maximize their effectiveness in treating the intended disease and to minimize their unintended side effects, e.g., so as to minimize their EC_{50} for inhibiting glucose intolerance and to maximize their EC_{50} for causing immunosuppression. The Balkan et al abstract teaches that administration of its DPP-IV inhibitor may be a useful tool in the treatment of NIDDM, but does not explicitly teach administering a DPP-IV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using a DPP-IV inhibitor suggested by the Balkan et al abstract as modified above by the WO Patent Application '309 to treat Type II diabetes, because the Balkan et al abstract discloses that this may be a viable approach to the management of diabetes by preventing the inactivation of endogenous GLP-1, because the Balkan et al abstract's rat model are predictive of in vivo success in humans due to their resemblance to humans in terms of physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes.

16. Claims 1-14, 16-24, 26, 27, and 29-40 are rejected under 35 U.S.C. 103(a) as being obvious over the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) in view of the WO Patent Application 93/08259 and further in view of Efendic et al. The Balkan et al abstract teaches improving the glucose tolerance of insulin resistant, glucose intolerant, obese Zucker rats

by administering the DPP-IV inhibitor SDZ 272-070 (i.e. valine pyrrolidide). The inhibitor prevents inactivation of endogenous GLP-1. The Balkan et al abstract does not disclose the use of DPIV inhibitors having a Ki and an EC_{50} as recited in claims 8-11 and 33-35, having oral activity, or having the structure recited in instant claims 1, 2, 4, 16-24, 26, 27, 30, 31 and 37. The WO Patent Application '259 teaches inhibiting the enzymatic activity of DPIV in a mammal by administering a peptide compound. The peptide compounds are proteolyzed by DPIV in vivo until a C-terminal dipeptide portion remains, which acts as an inhibitor of DPIV. The peptide compound is more stable in vivo than the C-terminal dipeptide portion. If the C-terminal dipeptide portion is chosen to be a dipeptide prolyl-boronic acid, then a potent and highly specific inhibitor having a Ki in the nanomolar range is ultimately released in vivo. Tetrapeptides comprising Ala-boroPro and Pro-boroPro as the C-terminal dipeptide portions are taught, as are boroPro analogues comprising groups capable of being hydrolyzed to form hydroxyl groups. As an alternative to the boroPro group, trifluoroalkyl ketone groups are taught. Administration can be oral. See, e.g., page 2, lines 15-32; page 3, line 1 - page 7, line 16; page 14, lines 10-12; page 14, line 34 - page 15, line 16; and page 21, line 15. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the DPIV inhibitors of the WO Patent Application '259 in the methods of the Deacon et al article or the Balkan et al abstract because the DPIV inhibitors of the WO Patent Application '259 have the advantage of having a low Ki and of having chemical stability, which would permit the use of smaller dosages of the active agent, because the DPIV inhibitors of the WO Patent Application '259 are described as being generally useful as inhibitors of DPIV-mediated processes (see, e.g., page 6, lines 4-10) and the methods of the Deacon et al article and the

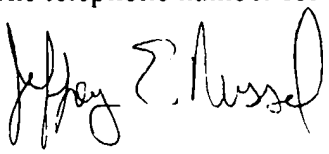
Balkan et al abstract operate via a DPIV-mediated process, and because the DPIV inhibitors of the WO Patent Application '259 can be administered orally, which is a more convenient and acceptable method of administration for the patient. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to choose DPIV inhibitors from the WO Patent Application '259 for use in the methods of the Deacon et al article or the Balkan et al abstract so as to maximize their effectiveness in treating the intended disease and to minimize their unintended side effects, e.g., so as to minimize their EC_{50} for inhibiting glucose intolerance and to maximize their EC_{50} for causing immunosuppression. The Balkan et al abstract teaches that administration of its DPP-IV inhibitor may be a useful tool in the treatment of NIDDM, but does not explicitly teach administering a DPP-IV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using a DPP-IV inhibitor suggested by the Balkan et al abstract as modified above by the WO Patent Application '259 to treat Type II diabetes, because the Balkan et al abstract discloses that these may be viable approaches to the management of diabetes by preventing the inactivation of endogenous GLP-1, because the Balkan et al abstract's rat model is predictive of in vivo success in humans due to their resemblance to humans in terms of physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes.

17. Applicant's arguments filed September 15, 2003 have been fully considered but they are not persuasive.

The anticipation rejections based upon the WO Patent Application 95/15309 and the WO Patent Application 93/08259 are maintained for the reasons of record. In addition, the Kieffer et al article (Endocrinology, Vol. 136, pages 3585-3596), the Mentlein et al article (Eur. J. Biochem., Vol. 214, pages 829-835), and Drucker et al (U.S. Patent No. 6,184,201) are now relied upon as additional evidence that the result recited in Applicants' claims would not be "accidental and unwitting" but rather would have been expected. Finally, a new set of rejections based upon the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) is presented which avoids the inherency issue.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
November 6, 2003